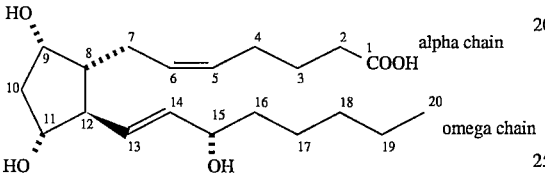
USE OF CLOPROSTENOL, FLUPROSTENOL AND THEIR SALTS AND ESTERS TO TREAT GLAUCOMA AND OCULAR HYPERTENSION

BACKGROUND OF THE INVENTION

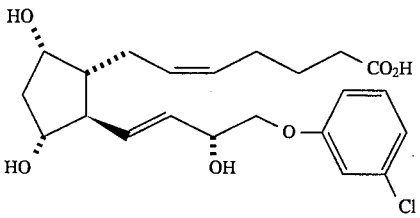
The present invention relates to the treatment of glaucoma and ocular hypertension. In particular, the present invention relates to the use of cloprostenol, fluprostenol, and their pharmaceutically acceptable salts and esters to treat glaucoma and ocular hypertension.

Cloprostenol and fluprostenol, both known compounds, are synthetic analogues of $PGF_{2\alpha}$, a naturally-occurring F-series prostaglandin (PG). Structures for $PGF_{2\alpha}$, cloprostenol, and fluprostenol, are shown below:

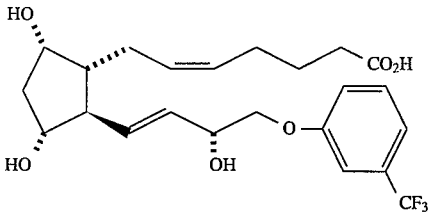
$PGF_{2\alpha}$:



Cloprostenol:



Fluprostenol:



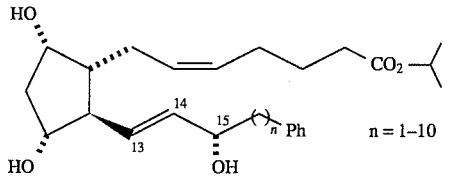
The chemical name for cloprostenol is 16-(3-chlorophenoxy)-17, 18, 19, 20-tetranor $PGF_{2\alpha}$. Monograph No. 2397 (page 375) of *The Merck Index,* 11th Edition (1989) is incorporated herein by reference to the extent that it describes the preparation and known pharmacological profiles of cloprostenol. Fluprostenol has the chemical name 16-(3-trifluoromethylphenoxy)-17, 18, 19,20-tetranor $PGF_{2\alpha}$. Monograph No. 4121 (pages 656–657) of *The Merck Index,* 1 1th Edition (1989) is incorporated herein by reference to the extent that it describes the preparation and known pharmacological profiles of fluprostenol. Cloprostenol and fluprostenol are 16-aryloxy PGs and, in addition to the substituted aromatic ring, differ from the natural product, $PGF_{2\alpha}$ in that an oxygen atom is embedded within the lower (omega) chain. This oxygen interruption forms an ether functionality.

Naturally-occurring prostaglandins are known to lower intraocular pressure (IOP) after topical ocular instillation, but generally cause inflammation, as well as surface irritation characterized by conjunctival hyperemia and edema.

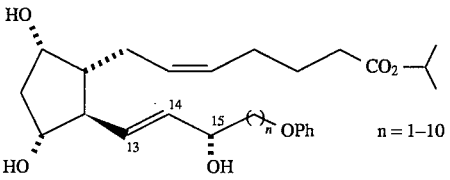
Many synthetic prostaglandins have been observed to lower intraocular pressure, but such compounds also produce the aforementioned side effects. Various methods have been used in attempting to overcome the ocular side effects associated with prostaglandins. Stjernschantz et al. (EP 364 417 A1) have synthesized derivatives or analogues of naturally-occurring prostaglandins in order to design out selectively the undesired side effects while maintaining the IOP-lowering effect. Others, including Ueno et al. (EP 330 511 A2) and Wheeler (EP 435 682 A2) have tried complexing prostaglandins with various cyclodextrins.

The Stjernschantz et al. publication is of particular interest, as it demonstrates that certain synthetically-modified $PGF_{2\alpha}$ analogues retain the potent IOP-lowering effect of the parent ($PGF_{2\alpha}$ isopropyl ester) while decreasing the degree of conjunctival hyperemia. In this publication, the only modification to the PG structure is to the omega chain: the chain length is 4–13 carbon atoms "optionally interrupted by preferably not more than two heteroatoms (O, S, or N)" and includes a phenyl ring (substituted or unsubstituted) on the terminus (see page 3, line 44 to page 4, line 7). Stjernschantz et al. exemplify two subclasses within this definition:

(1) carbon-only omega chains, i.e.,



and (2) heteroatom-interupted omega chains, i.e.,



In particular, the 17-phenyl-18, 19,20-trinor analogue of $PGF_{2\alpha}$ isopropyl ester (formula 1, n=2) displayed a superior separation of toward and untoward activities. Furthermore, the 13, 14-dihydro analogue of 17-phenyl-18, 19,20-trinor $PGF_{2\alpha}$ isopropyl ester displayed an even more favorable separation of activities. Both 17-phenyl $PGF_{2\alpha}$ and its 13, 14-dihydro congener fall into the former (formula 1, carbon-only omega chain) subclass. Additional synthetic analogues employing the phenyl substituent on the end of the omega chain explored the effects of chain elongation, chain contraction, and substitution on the phenyl ring. However, such analogues showed no apparent therapeutic improvement over the preferred formulation, 13, 14-dihydro-17-phenyl-18, 19,20-trinor $PGF_{2\alpha}$ isopropyl ester.

Because they contain heteroatom (O) interruption of the omega chain, both cloprostenol and fluprostenol are generically included in the subclass defined in formula 2 by Stjernschantz et al. However, neither compound is specifically mentioned by Stjernschantz et al. and the disclosure is primarily related to carbon-only omega chains. The only example of a heteroatom-interrupted omega chain disclosed by Stjernschantz et al. is 16-phenoxy-17,18,19,20 tetranor $PGF_{2\alpha}$ isopropyl ester (see formula 2, n=1). The IOP data revealed by Stjernschantz et al. for 16-phenoxy-17, 18, 19,20-tetranor $PGF_{2\alpha}$ isopropyl ester (see Stjernschantz et al, page 17, Table V) indicate an initial increase in IOP (1–2